Clinical Medicine

Nosocomial Pneumonia in Patients in Intensive Care Units

STEVEN D. PODNOS, MD; GALEN B. TOEWS, MD, *and* ALAN K. PIERCE, MD, *Dallas*

Nosocomial pneumonia is a major cause of mortality among patients in intensive care units, despite recent advances in antimicrobial therapy. Aerobic Gram-negative bacilli remain the pathogens responsible for most of these pneumonias. These organisms colonize the oropharynx of severely ill patients, and their subsequent aspiration results in lower respiratory tract infection. Recent investigation into the pathogenesis of oropharyngeal bacterial colonization has shown the central importance of bacterial adherence mechanisms.

(Podnos SD, Toews GB, Pierce AK: Nosocomial pneumonia in patients in intensive care units. West J Med 1985 Nov; 143:622-627)

Sophisticated therapies in intensive care units allow many patients to survive a primary illness, only to succumb to nosocomial infection. Pneumonia is now the most common hospital-acquired infection leading to death, occurring in 0.5% to 5% of all in-hospital patients and in 12% to 15% of patients ill enough to require intensive care.[1-3] The incidence of pneumonia in the intensive care unit (ICU) setting is related to the primary disease process; rates of 5% for patients with cardiovascular disease, 24% for primary respiratory tract disease and 63% for acute respiratory failure have been reported.[2,4]

Gram-negative bacilli (GNB) are the pathogens responsible for nosocomial pneumonia in 75% to 90% of cases, with *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli* and *Proteus* species the most commonly isolated agents.[1,5,7] In a study of patients in ICUs, pneumonia due to Gram-positive cocci did not add significantly to the usual mortality of 4% to 5%, while that caused by GNB resulted in a mortality of 33%; a 70% mortality occurred if *P aeruginosa* was present.[8] Anaerobic bacteria have not been recovered despite careful techniques in two recent studies of nosocomial pneumonia.[9,10] In this review we will address recent advances in the attempt to diagnose, treat and prevent these increasingly important bacterial infections. *Legionella* species have been noted to cause epidemic nosocomial pneumonia in certain hospitals. In most intensive care units, however, *Legionella* species and other newly recognized agents that may be responsible for nosocomial pneumonia constitute less than 5% of all cases and will not be discussed here.[11-15]

Pathogenesis

An alteration in bacterial colonization of the oropharynx is the most important factor responsible for the increased incidence of and change in the bacterial species responsible for pneumonia in patients in ICUs. In a baboon model of acute respiratory failure, 9 of 11 animals were shown to have GNB oropharyngeal colonization before the onset of GNB pneumonia.[16] As many as 90% of patients in ICUs in whom pneumonia develops have an earlier oropharyngeal colonization with the same species of GNB.[1,2] Pneumonia develops in 12% to 25% of all patients so colonized, whereas only 3% of patients not previously colonized have this complication.[2]

The risk of colonization of the pharynx with GNB is related to the general state of health of the population studied. Gram-negative bacilli are rarely cultured from the oropharynx of healthy persons.[17-19] In experimental animals, starvation for three days results in a pronounced increase in GNB colonization.[20] A third of healthy patients become colonized with GNB 48 hours after a major surgical procedure.[21] About 17% of moderately ill and 55% of severely ill patients are colonized at the time of admission to an ICU.[17] Acute respiratory failure is associated with an especially high risk of GNB colonization and pneumonia. In all of the animals in a recent study of a model of the adult respiratory distress syndrome, GNB oropharyngeal colonization and subsequent pneumonia developed.[16] In all, 74% of patients who die of the adult respiratory distress syndrome have histologic proof of pneumonia at autopsy.[22] Specific risk factors for colonization include coma, acidosis, alcoholism, diabetes mellitus, hypo-

From the Pulmonary Division, Department of Internal Medicine, Parkland Hospital and The University of Texas Southwestern Medical School at Dallas.

Submitted, revised, January 28, 1985.

This study was funded in part by the Robert Patrick Thompson Fund.

Reprint requests to Steven D. Podnos, MD, Pulmonary Division, Dept of Internal Medicine, The University of Texas Health Science Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235.

ABBREVIATIONS USED IN TEXT
GNB = Gram-negative bacilli
ICU = intensive care unit
TPC = telescoping protected [brush] catheter

tension, leukocytosis, leukopenia, azotemia, primary respiratory tract disease, endotracheal intubation and possibly the prophylactic use of antibiotics.[2,23,24] The duration of ICU stay is not a significant risk factor for colonization, as the majority of patients who become colonized do so by the fourth hospital day. Sources of the GNB appear to be gastrointestinal organisms endogenous to a colonized patient and GNB transmitted from other patients by hospital personnel.[25]

Bacterial adherence to epithelial cells is of central importance to the pathogenesis of oropharyngeal GNB colonization, a phenomenon previously found in patients with urinary and gastrointestinal tract infections.[26,27] Gram-positive organisms normally colonize the oropharyngeal area and may protect against adherence and colonization by GNB. Patients who become colonized have fewer Gram-positive cocci and larger numbers of GNB adherent per epithelial cell.[21]

Fibronectin, a 200,000-dalton cell surface glycoprotein, may be the factor regulating GNB adherence and colonization. Gram-positive cocci bind well to cells rich in fibronectin, whereas GNB bind well only to cells that are fibronectin deficient.[28,29] GNB attach to sugar-containing sites on the cell membrane by means of fingerlike projections on their surface called pili. Fibronectin probably protects against GNB adherence by blocking these sites.[30,31] Trypsinized oropharyngeal cells from healthy volunteers and unmodified cells taken from GNB-colonized patients are both remarkable for decreased concentrations of cell surface fibronectin, as well as an increased ability to bind GNB.[31,32] A prospective study of healthy patients undergoing elective surgical procedures showed an increase in salivary protease activity following the operation, accompanied by a decrease in cell surface fibronectin and an increased *Pseudomonas*-cell binding ratio.[33] It is not clear whether salivary protease activity is augmented by host or microbial sources or by a decreased amount of a normally present protease-inhibitor.

The ICU environment also may be important in the pathogenesis of nosocomial pneumonia. Potential colonization of respiratory support equipment has been shown as an important, yet preventable, source of this nosocomial infection.[1,5,34,35] Invasive catheters and urinary drainage devices allow a nidus of lymphohematogenous spread of infection, although this remains a relatively uncommon cause of pneumonia.[1,2] In an autopsy series of patients with the adult respiratory disease syndrome, however, a third of the cases of pneumonia found were felt to be secondary processes, with peritoneal abscesses the most common primary site of infection.[22] Interpatient transfer of bacteria by hospital personnel, including poor hand-washing patterns by physicians, may result in an increased incidence of infection with resistant organisms.[36]

Diagnosis

Even if a nosocomial pneumonia is suspected on the basis of fever, leukocytosis and a new infiltrate on chest radiography, the presence of infection is not certain. In two recent studies, the use of clinical and radiologic signs and the response to therapy to diagnose the presence of pneumonia in patients with diffuse lung injury resulted in a 30% to 45% incidence of false-positive and false-negative diagnoses.[22,37] Thus, most clinicians initiate antibiotic therapy upon any suspicion of nosocomial pneumonia, given the risks of untreated infection. Diagnostic methods are most useful for identifying an organism responsible for the pneumonia in order to guide specific therapy. Numerous authors have reviewed the use of various diagnostic techniques toward this goal.[1,5,38-41] While bacteria are the most common etiologic agents in nosocomial pneumonia, patients with certain malignant lesions, those with neutropenia and patients taking immunosuppressive medications or with congenital or acquired immunocompromising diseases are at additional risk for pneumonia caused by a wide spectrum of opportunistic organisms. Indeed, pneumonia is the most common site of serious infection in these hosts. The additional complexity involved in isolating and treating the fungi, viruses and parasites that can infect these patients often requires a more aggressive diagnostic approach. Readers are referred to several excellent reviews of pneumonia in an immunosuppressed host, and we will focus on cases of generally immunocompetent patients.[39-45]

The initial diagnostic intervention should be to obtain specimens for culture from sites that are most likely to provide a definitive diagnosis. Several blood specimens should be obtained for culture. If pleural fluid is present in sufficient quantity to be safely aspirated, it should be examined by Gram's stain and culture. If an organism is identified from these sources, therapy can then be specifically directed. Unfortunately, the use of expectorated sputum to identify an infectious agent may not be reliable, as it is virtually impossible to separate bacteria that colonize the oropharynx from those responsible for the pneumonia. Expectorated sputum is often not representative of lower respiratory tract secretions.[46,47] Methods of "grading" the quality of expectorated sputum and quantitative culture techniques have not proved accurate in patients in ICUs.[41,46-50] Sputum obtained by transtracheal aspiration or by suction (nasotracheally or through a tracheostomy or endotracheal tube) theoretically allows sampling of tracheal secretions without oropharyngeal contamination. Although transtracheal aspiration has been extensively studied in cases of community-acquired pneumonia,[49-55] it has not been selectively studied in patients with hospital-acquired infection. Also, both suctioned sputum and transtracheal aspirate may be contaminated with a trachea-colonizing flora, which may not represent the cause of the pneumonia.[49,51,56-58]

In recent studies new techniques have been used to bypass the upper respiratory tract and thus obtain uncontaminated lower tract secretions. Specimens taken by brushing and suctioning using standard fiberoptic bronchoscopy are frequently contaminated by bacteria that colonize the oropharynx.[59-62] The combination of quantitative cultures and immunofluorescent staining techniques was recently found to significantly increase the sensitivity and specificity of cultures obtained in this fashion.[63] As few patients were receiving antibiotics and few had other bacteriologic proof of pneumonia, further evaluation of these techniques is needed in an ICU population before they can be recommended.

A "wedged" catheter technique for use in intubated patients has recently been evaluated in cases of community-acquired pneumonia, with encouraging results.[64] Controlled studies in patients with hospital-acquired pneumonia are needed before this technique can be recommended in the ICU population. The telescoping protected brush catheter (TPC) inserted through a fiberoptic bronchoscope has recovered sterile lower tract secretions in healthy patients.[59,60,65] Because low concentrations of oropharyngeal organisms can be taken from the lower respiratory tract of some healthy volunteers, quantitative culture techniques are important when using the TPC.[9,61,62,66] In a comparison of diagnostic techniques using a dog model of pneumococcal pneumonia, the TPC showed a sensitivity and specificity second only to transthoracic lung puncture.[56] In patients with community-acquired pneumonia, TPC recovered the same organisms found in all bacteremic patients.[67] In a study of primates with nosocomial pneumonia, the TPC was 70% sensitive and 90% specific.[10] Further evidence of the sensitivity of this technique is provided by a recent study that compared quantitative cultures of specimens obtained with the TPC and by lung biopsy in patients who died while on mechanical ventilation. All specimens were obtained immediately after the death of the patient. TPC cultures identified every bacteria present in every patient with histologic proof of pneumonia. There were some false-positive culture results, but no case of pneumonia was missed with the TPC.[9] Unfortunately, a recent comparison of the TPC, transthoracic lung puncture and the use of a regular cytology brush in patients with underlying diseases admitted for acute pulmonary infections had less encouraging results.[68]

Thus, studies of various techniques of obtaining specimens by fiberoptic bronchoscopy have yielded variable results or the techniques have not been adequately tested in ICU patients. Further, although fiberoptic bronchoscopy is a safe procedure in ambulatory patients,[69] its use in critically ill patients often results in a higher rate of complications.[70] For these reasons, most physicians do not routinely use these techniques.

More invasive diagnostic modalities—direct lung aspiration and open-lung biopsy—have been studied predominantly in immunocompromised hosts.[3,39-44,49] These procedures carry a significant risk of complications, and no data are available to support their use in nonimmunosuppressed ICU patients.

Clinical Approach and Therapy

In a patient with presumed nosocomial pneumonia and no pathogen seen on Gram's stain of a pleural fluid specimen, sputum is the only material available on which to make therapeutic decisions. Although sputum is often contaminated with organisms not responsible for the nosocomial pneumonia, careful evaluation of a Gram's stain may indicate the need for broader antimicrobial coverage if an unsuspected pathogen such as *Hemophilus influenzae* is seen. This organism is a small Gram-negative coccobacillus that may cause community- or hospital-acquired pneumonia.[9,64] If blood, pleural fluid and sputum specimens are not diagnostic, the clinician must decide whether or not to proceed to more invasive diagnostic procedures. One or more of these procedures may be helpful in the initial diagnosis or after failure of empiric therapy. Each procedure has risks, and the physician must weigh the possible morbidity against the probabilities of obtaining useful therapeutic information. In most instances, the initial choice of antimicrobial therapy is empiric.

Recommended empiric therapy is the use of two antimicrobial agents to cover the wide spectrum of organisms (with variable antimicrobial resistance) responsible for nosocomial pneumonia. The combination of an aminoglycoside with an extended-spectrum penicillin or a cephalosporin will accomplish these goals in most instances.[71-75] An apparent *H influenzae* on sputum Gram's stain mandates coverage of this organism as well. Third-generation cephalosporins may offer improved coverage of GNB with less nephrotoxicity than aminoglycosides. Cefotaxime sodium and cefoperazone sodium may be the most useful of this group for the treatment of patients with hospital-acquired pneumonia (Table 1).[73-78] In a recent trial, cefotaxime was found to be more effective and less toxic than the combination of nafcillin sodium and tobramycin in treating patients with serious bacterial infections.[78] Further studies are required, however, before single-drug empiric therapy can be recommended for patients with hospital-acquired pneumonia. Suspected infection with *P aeruginosa* (as in hospital epidemics) requires additional coverage with an extended-spectrum penicillin or cefoperazone.[70-74] At this time, more specific choices of antimicrobial drugs cannot be generalized from the literature. The bacterial flora of each hospital and its antimicrobial sensitivities should be used as a guide in making individual drug decisions. Unfortunately, the previously noted high mortality rates for Gram-negative nosocomial pneumonia occur in spite of antimicrobial therapy.[8,72,73]

If a pathogen is subsequently cultured from blood or pleural fluid specimens, specific antimicrobial therapy may be used and inappropriate agents dropped from the regimen. Efficacy of antibiotic therapy in patients with bacteremia may be predicted by measuring peak serum bactericidal concentra-

TABLE 1.—*Third-Generation Cephalosporins Useful in Empiric Therapy for Nosocomial Pneumonia*

Drug Name	Excretion	IV Dose in Adults
Cefoperazone sodium . .	Biliary	2 grams q 4-12 h*
Cefotaxime sodium	Renal	2 grams q 4-6 h*

IV = intravenous

*In treating severely ill patients, both drugs should be given every 4 h.

TABLE 2.—*Aminoglycoside Plasma Concentrations Associated With Improved Response in Cases of Gram-Negative Pneumonia**

Drug Therapy†	1-H Postinfusion Plasma Levels: Maximal Peak μg/ml	1-H Postinfusion Plasma Levels: Mean Peak μg/ml
Gentamicin sulfate/tobramycin . .	≥ 7	≥ 6
Amikacin sulfate	≥ 28	≥ 24

*From Moore et al.[80]

†Aminoglycosides were used in combination with a penicillin or cephalosporin in fixed doses.

tions.[79] Achieving certain peak aminoglycoside levels has been shown to improve the outcome of patients with GNB pneumonia (Table 2).[80] Although results of culture of expectorated or suctioned sputum may be used to initiate broader antimicrobial coverage, they are not reliable enough alone to allow discontinuation of empiric coverage.

In a single study, endotracheally administered sisomicin sulfate, in addition to standard intravenous antibiotic therapy in patients with nosocomial GNB pneumonia, resulted in a decrease in mortality without toxic effects or emergence of drug-resistant organisms.[81] Systemic levels of sisomicin were not affected by the endotracheal dose, suggesting the importance of antibiotic concentration locally in determining the efficacy of therapy.[82] Confirmation of these results is necessary before this therapy can be recommended.

Prevention

Although effective infection control measures cannot prevent oropharyngeal colonization of susceptible patients, they may prevent GNB already resistant to antimicrobials from entering a patient's environment. These methods include hand-washing after contact with each patient and proper sterilization of respiratory therapy equipment.[1,34,36]

Because most cases of nosocomial pneumonia are preceded by oropharyngeal colonization with Gram-negative bacteria (GNB), research has focused on preventing such colonization. Trials of the prophylactic use of parenteral antibiotics to prevent hospital-acquired pneumonia resulted in the emergence of antibiotic-resistant organisms.[83] Efforts were next directed at prophylactically using antibiotics locally in the oropharyngeal region. Even minimal doses of antibiotics can alter the structure and function of bacterial "adhesins" (bacterial structures involved in binding to cells) and thereby prevent bacterial-cellular binding.[84,85] Between 1970 and 1975, three trials using prophylactic polymyxin B sulfate aerosolized into the oropharynx of ICU patients showed a significant decrease in colonization with GNB.[86-88] One trial of continuous polymyxin B use resulted in pneumonias caused by predominantly polymyxin-resistant bacteria. No trial showed a significant decrease in mortality. An additional three trials using endotracheally administered gentamicin sulfate to prevent infection in patients with tracheostomies resulted in no improvement in overall mortality.[89-91] Unfortunately, there was a significantly increased incidence of gentamicin-resistant organisms in the antibiotic-treated groups. Aerosolized gentamicin had no effect on infectious complications or mortality in a prospective randomized study of patients with inhalation burn injuries.[92] In a recent study of acute respiratory failure in animals, the combination of intensive oropharyngeal suctioning, topical polymyxin B and systemic ampicillin lowered the attack rate of GNB pneumonia to 19%, compared with 100% in control animals. Overall mortality was not stated, and ampicillin therapy was begun before respiratory failure. However, these findings support the rationale for altering the oropharyngeal environment in seriously ill patients.[16]

Early trials of an anti-*Pseudomonas* vaccine were effective in lowering the prevalence of *Pseudomonas* colonization and infection in susceptible patients, but there was no effect on mortality.[93-96] A newer anti-*Pseudomonas* vaccine has shown more encouraging results in burn patients.[97-98] A human vaccine composed of the core lipopolysaccharide shared by most clinically important GNB had significant protective effect in immunosuppressed animals.[99] Passive immunization using human antiserum produced by vaccinating healthy volunteers decreased mortality in patients with GNB bacteremia.[99,100] Unfortunately, it will require more investigation before these techniques are available for use and proved to be effective in patients in ICUs.

Other methods to prevent colonization by Gram-negative bacteria will use knowledge gained from studying bacterial adherence. Future therapeutic modalities may involve isolated cell receptor analogues or isolated bacterial adhesin analogues to interfere in the binding process. Alternatively, the increased protease activity in saliva of colonization-susceptible patients could be neutralized to prevent the loss of fibronectin, or a method to restore already lost fibronectin may be developed.

Summary

Nosocomial bacterial pneumonia remains a major cause of mortality in ICU patients. In patients not responding to empiric therapy, new diagnostic techniques involving bronchoscopically placed protected catheters may allow more specific isolation of causative agents and may thereby improve the efficacy of current antibiotic therapy. Future advances in this field should focus on preventing these infections, using knowledge gained from an orderly sequence of recent investigations. These studies have shown that severe illness results in a loss of fibronectin from oropharyngeal cell surfaces. GNB colonization follows, and aspiration of oropharyngeal bacteria leads to GNB pneumonia. Using this knowledge at a molecular and cellular level may allow interruption of GNB colonization and thereby GNB pneumonia. Alternatively, future vaccines may provide effective prophylaxis against these infections.

REFERENCES

1. Sanford JP, Pierce AK: Lower respiratory tract infections, *In* Bennett J, Brachtman P (Eds): Hospital Infections. Boston, Little, Brown, 1979, pp 255-286

2. Johanson WG Jr, Pierce AK, Sanford JP, et al: Nosocomial respiratory infections with Gram-negative bacilli. Ann Intern Med 1972; 77:701-706

3. Palmer DL: Microbiology of pneumonia in the patient at risk. Am J Med 1984; 76(suppl):53-60

4. Gross PA, Neu HC, Aswapokee P, et al: Deaths from nosocomial infections: Experience in a university hospital and a community hospital. Am J Med 1980; 68:219-223

5. Jay SJ: Nosocomial infections. Med Clin North Am 1984; 67:1251-1277

6. Valdivieso M, Gil-Extremera B, Zornoza J, et al: Gram-negative bacillary pneumonia in the compromised host. Medicine (Baltimore) 1977; 56:241-254

7. Ashbaugh DG, Petty TL: Sepsis complicating the acute respiratory distress syndrome. Surg Gynecol Obstet 1972; 135:865-869

8. Stevens RM, Teres D, Skillman JJ, et al: Pneumonia in an intensive care unit. Arch Intern Med 1974; 134:106-111

9. Chastre J, Viau F, Brun P, et al: Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am Rev Respir Dis 1984; 130:924-929

10. Higushi JH, Coalson JJ, Johanson WG Jr: Bacteriologic diagnosis of nosocomial pneumonia in primates: Usefulness of the protected specimen brush. Am Rev Respir Dis 1982; 125:53-57

11. Fick RB, Reynolds HY: Changing spectrum of pneumonia, news media creation or clinical reality? Am J Med 1983; 74:1-8

12. Fraser DW: Bacteria newly recognized as nosocomial pathogens. Am J Med 1981; 70:432-438

13. Yu VL, Kroboth FJ, Shonnard J, et al: Legionnaire's disease: New clinical perspectives from a prospective pneumonia study. Am J Med 1982; 73:357-361

14. Cohen ML, Broome CV, Paris AL, et al: Fatal nosocomial legionnaire's disease: Clinical and epidemiologic characteristics. Ann Intern Med 1979; 90:611-613

15. Yu VL, Zuravleff JJ, Elder EM, et al: Pittsburgh pneumonia agent may be a common cause of nosocomial pneumonia: Seroepidemiologic evidence. Ann Intern Med 1982; 97:724-726

16. Crouch TW, Higuchi JH, Coalson JJ, et al: Pathogenesis and prevention of

nosocomial pneumonia in a nonhuman primate model of acute respiratory failure. Am Rev Respir Dis 1984; 130:502-504

17. Johanson WG Jr, Pierce AK, Sanford JP: Changing pharyngeal bacterial flora of hospitalized patients. N Engl J Med 1969; 281:1137-1140

18. Valenti WM, Trudell RG, Bentley DW: Factors predisposing to oropharyngeal colonization with gram-negative bacilli in the aged. N Engl J Med 1978; 298:1108-1111

19. LaForce FM, Hopkins J, Trow R, et al: Human oral defenses against gram-negative rods. Am Rev Respir Dis 1976; 114:929-935

20. Higuchi JH, Johanson WG Jr: The relationship between adherence of *Pseudomonas aeruginosa* to upper respiratory cells in vitro and susceptibility to colonization in vivo. J Lab Clin Med 1980; 95:698-705

21. Johanson WG Jr, Higushi JH, Chaudhuri TR, et al: Bacterial adherence to epithelial cells in bacillary colonization of the respiratory tract. Am Rev Respir Dis 1980; 121:55-63

22. Bell R, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293-298

23. Mackowiak PA, Martin RM, Jones SR, et al: Pharyngeal colonization by gram-negative bacilli in aspiration-prone persons. Arch Intern Med 1978; 138:1224-1227

24. Mackowiak PA, Martin RM, Smith JW: The role of bacterial interference in the increased prevalence of oropharyngeal gram-negative bacilli among alcoholics and diabetics. Am Rev Respir Dis 1979; 120:589-593

25. Selden R, Lee S, Wang WLL, et al: Nosocomial klebsiella infections: Intestinal colonization as a reservoir. Ann Intern Med 1971; 74:657-664

26. Fowler JE Jr, Stamey TA: Studies on introital colonization in women with recurrent urinary tract infections. J Urol 1977; 117:472-476

27. Jones GW, Rutter JM: Role of the K88 antigen in the pathogenesis of neonatal diarrhea caused by E. coli in piglets. Infect Immun 1972; 6:918-927

28. Abraham SN, Beachey EH, Simpson WA: Adherence of *Streptococcus pyogenes, Escherichia coli,* and *Pseudomonas aeruginosa* to fibronectin-coated and uncoated epithelial cells. Infect Immun 1983; 41:1261-1268

29. Woods DE, Bass JA, Johanson WG Jr, et al: Role of adherence in the pathogenesis of *Pseudomonas aeruginosa* lung infection in cystic fibrosis patients. Infect Immun 1980; 30:694-699

30. Johanson WG Jr, Woods DE, Chaudhuri T: Association of respiratory tract colonization with adherence of gram-negative bacilli to epithelial cells. J Infect Dis 1979; 139:667-673

31. Ofek I, Mirelman D, Sharon N: Adherence of E coli to human mucosal cells mediated by mannose receptors. Nature 1977; 265:623-625

32. Woods DE, Straus DC, Johanson WG Jr, et al: Role of fibronectin in the prevention of adherence of *Pseudomonas aeruginosa* to buccal cells. J Infect Dis 1981; 143:784-790

33. Woods D, Straus DC, Johanson WG Jr, el al: Role of salivary protease activity in adherence of gram-negative bacilli to mammalian buccal epithelial cells in vivo. J Clin Invest 1981; 68:1435-1440

34. Pierce AK, Sanford JP, Thomas GD, et al: Long term evaluation of decontamination of inhalation-therapy equipment and the occurrence of necrotizing pneumonia. N Engl J Med 1970; 282:528-531

35. Craven DE, Lichtenberg DA, Goularte TA, et al: Contaminated medication nebulizers in mechanical ventilation circuits. Am J Med 1984; 77:834-838

36. Albert RK, Condie F: Hand-washing patterns in medical intensive-care units. N Engl J Med 1981; 304:1465-1466

37. Andrews CP, Coalson JJ, Smith JD, et al: Diagnosis of nosocomial bacterial pneumonia in acute diffuse lung injury. Chest 1981; 80:254-258

38. Pennington JE, Feldman NT: Pulmonary infiltrates and fever in patients with hematologic malignancy. Am J Med 1977; 62:581-587

39. Matthay RA, Moritz ED: Invasive procedures for diagnosing pulmonary infection. Clin Chest Med 1981; 2:3-18

40. Burt ME, Flye MW, Webber BL, et al: Prospective evaluation of aspiration needle, cutting needle, transbronchial, and open lung biopsy in patients with pulmonary infiltrates. Ann Thor Surg 1981; 32:146-153

41. Singer C, Armstrong D, Rosen PP, et al: Diffuse pulmonary infiltrates in immunosuppressed patients. Am J Med 1979; 66:110-120

42. Sagel SS, Ferguson TB, Forrest JV, et al: Percutaneous transthoracic aspiration needle biopsy. Ann Thor Surg 1978; 26:399-403

43. Berquist TH, Bailey PB, Cortese DA, et al: Transthoracic needle biopsy. Mayo Clin Proc 1980; 55:475-481

44. Leight GS, Michaelis LL: Open lung biopsy for the diagnosis of acute, diffuse pulmonary infiltrates in the immunosuppressed patient. Chest 1978; 73:477-482

45. Fanta CH, Pennington JE: Pneumonia in the immunocompromised host, *In* Pennington JE (Ed): Respiratory Infections: Diagnosis and Management. New York, Raven Press, 1983, pp 171-185

46. Murray PR, Washington JA: Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc 1975; 50:339-344

47. Guckian JC, Christensen WD: Quantitative culture and gram stain of sputum in pneumonia. Am Rev Respir Dis 1978; 118:997-1005

48. Barrett-Connor E: The nonvalue of sputum culture in the diagnosis of pneumococcal pneumonia. Am Rev Respir Dis 1971; 103:845-848

49. Davidson M, Tempest B, Palmer DL: Bacteriologic diagnosis of acute pneumonia—Comparison of sputum, transtracheal aspirates and lung aspirates. JAMA 1976; 235:158-163

50. Bartlett JG, Finegold SM: Bacteriology of expectorated sputum with quantitative culture and wash technique compared to transtracheal aspirates. Am Rev Respir Dis 1978; 117:1019-1027

51. Hahn HH, Beatty HN: Transtracheal aspiration in the evaluation of patients with pneumonia. Ann Intern Med 1970; 72:183-187

52. Bartlett JG: Diagnostic accuracy of transtracheal aspiration bacteriologic studies. Am Rev Respir Dis 1977; 115:777-782

53. Ries K, Levison ME, Kaye D: Transtracheal aspiration in pulmonary infections. Arch Intern Med 1974; 133:453-458

54. Schreiner A, Digranes A, Myking O: Transtracheal aspiration in the diagnosis of lower respiratory tract infections. Scand J Infect Dis 1972; 4:49-52

55. Kalinske RW, Parker RH, Brandt D, et al: Diagnostic usefulness and safety of transtracheal aspiration. N Engl J Med 1967; 276:604-608

56. Moser KM, Maurer J, Jassy L, et al: Sensitivity, specificity and risk of diagnostic procedures in a canine model of Streptococcus pneumonia. Am Rev Respir Dis 1982; 125:436-442

57. Neiderman MS, Ferranti RD, Zeigler A, et al: Respiratory infection complicating long-term tracheostomy. Chest 1984; 85:39-44

58. Neiderman MS, Rafferty RD, Sasaki CT, et al: Comparison of bacterial adherence to ciliated and squamous epithelial cells obtained from the human respiratory tract. Am Rev Respir Dis 1983; 127:85-90

59. Hayes DA, McCarthy LC, Friedman M: Evaluation of two bronchofiberoscopic methods of culturing the lower respiratory tract. Am Rev Respir Dis 1980; 122:319-323

60. Joshi JH, Wang K, DeJongh CA, et al: A comparative evaluation of two fiberbronchoscopic catheters: The plugged telescoping catheter versus the single sheathed non-plugged catheter. Am Rev Respir Dis 1982; 126:860-863

61. Flatauer FE, Chabalko JJ, Wolinsky E: Fiberoptic bronchoscopy in bacteriologic assessment of lower respiratory tract secretions—Importance of microscopic examination. JAMA 1980; 244:2427-2429

62. Teague RB, Wallace RJ, Awe RJ: The use of quantitative sterile brush culture and Gram stain analysis in the diagnosis of lower respiratory tract infection. Chest 1981; 79:157-161

63. Winterbauer RH, Hutchinson JF, Reinhardt GN, et al: The use of quantitative cultures and antibody coating of bacteria to diagnose bacterial pneumonia by fiberoptic bronchoscopy. Am Rev Respir Dis 1983; 128:98-103

64. Matthew EB, Holstrom FMG, Kaspar RL: A simple method for diagnosing pneumonia in intubated or tracheostomized patients. Crit Care Med 1977; 5:76-81

65. Wimberley N, Faling FJ, Bartlett JG: A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am Rev Respir Dis 1979; 119:337-343

66. Halperin SA, Suratt PM, Gwaltney JM Jr, et al: Bacterial cultures of the lower respiratory tract in normal volunteers with and without experimental rhinovirus infection using a plugged double catheter system. Am Rev Respir Dis 1982; 125:678-680

67. Wimberley NW, Bass JB, Boyd BW, et al: Use of a bronchoscopic protected catheter brush for the diagnosis of pulmonary infections. Chest 1982; 81:556-562

68. Fletcher EC, Mohr JA, Levin DC, et al: Bronchoscopic diagnosis of pulmonary infections: Comparison of protected-specimen brush and cytology brush with lung aspirates. West J Med 1983; 138:364-370

69. Credle WF, Smiddy JF, Elliott RC: Complications of fiberoptic bronchoscopy. Am Rev Respir Dis 1974; 109:67-72

70. Lindholm CE, Ollman B, Snyder JV, et al: Cardiorespiratory effects of flexible fiberoptic bronchoscopy in critically ill patients. Chest 1978; 74:362-368

71. Hirschmann JV, Murray JF: Pneumonia and lung abscess, *In* Petersdorf RG, Adams RD, Braunwald E, et al (Eds): Harrison's Principles of Internal Medicine, 10th Ed. New York, McGraw Hill, 1983, pp 1532-1539

72. Bryan CS, Reynolds KL: Bacteremic nosocomial pneumonia. Am Rev Respir Dis 1984; 129:668-671

73. Young LS: Treatment of respiratory infections in the patient at risk. Am J Med 1984; 76(suppl):61-68

74. Crane LR, Lerner AM: Gram-negative bacillary pneumonias, *In* Pennington JE (Ed): Respiratory Tract Infections. New York, Raven Press, 1983, pp 227-250

75. The choice of antimicrobial drugs. Lett Drugs Ther 1984; 26:19-26

76. Cunha BA, Ristuccia AM: Third-generation cephalosporins. Med Clin North Am 1982; 66:283-291

77. Neu HC: The new beta-lactamase stable cephalosporins. Ann Intern Med 1982; 97:408-419

78. Smith CR, Ambinder R, Lipsky JJ, et al: Cefotaxime compared with nafcillin plus tobramycin for serious bacterial infections. Ann Intern Med 1984; 101:469-477

79. Sculier JP, Klastersky J: Significance of serum bactericidal activity in gram-negative bacillary bacteremia in patients with and without granulocytopenia. Am J Med 1984; 76:429-434

80. Moore RD, Smith CR, Lietman PS: Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am J Med 1984; 77:657-662

81. Klastersky J, Carpentier-Meunier F, Kahan-Coppens J, et al: Endotracheally administered antibiotics for gram-negative bronchopneumonia. Chest 1979; 75:586-591

82. Smith BR, LeFrock JL: Bronchial tree penetration of antibiotics. Chest 1983; 83:904-908

83. Petersdorf RG, Curtin JA, Hoeprich PD, et al: A study of antibiotic prophylaxis in unconscious patients. N Engl J Med 1957; 257:1001-1009

84. Beachey EH: Bacterial adherence: Adhesin-receptor interactions mediating the attachment of bacteria to mucosal surfaces. J Infect Dis 1981; 143:325-345

85. Eisenstein BI, Ofek I, Beachey EH: Interference with the mannose binding and epithelial cell adherence of *Escherichia coli* by sublethal concentrations of streptomycin. J Clin Invest 1979; 63:1219-1228

86. Greenfield S, Teres D, Bushnell LS, et al: Prevention of gram-negative bacillary pneumonia using aerosol polymyxin as prophylaxis: I. Effect on the colonization

pattern of the upper respiratory tract of seriously ill patients. J Clin Invest 1973; 52:2935-2940

87. Klick JM, DuMoulin GC, Hedley-White J, et al: Prevention of gram-negative bacillary pneumonia using aerosol polymyxin as prophylaxis: II. Effect on the incidence of pneumonia in seriously ill patients. J Clin Invest 1975; 55:514-519

88. Feeley TW, DuMoulin GC, Hedley-White J, et al: Aerosol polymyxin and pneumonia in seriously ill patients. N Engl J Med 1975; 293:471-475

89. Klastersky J, Geuning C, Mouawad E, et al: Endotracheal gentamicin in bronchial infections in patients with tracheostomy. Chest 1972; 61:117-120

90. Klastersky J, Huysmans E, Weerts D, et al: Endotracheally administered gentamicin for the prevention of infections of the respiratory tract in patients with tracheostomy: A double blind study. Chest 1974; 65:650-654

91. Klastersky J, Hensgens C, Noterman J, et al: Endotracheal antibiotics for the prevention of tracheobronchial infections in tracheotomized unconscious patients—A comparative study of gentamicin and aminosidin-polymyxin B combination. Chest 1975; 68:302-306

92. Levine BA, Petroff PA, Slade CL, et al: Prospective trials of dexamethasone and aerosolized gentamicin in the treatment of inhalation injury in the burned patient. J Trauma 1978; 18:188-193

93. Young LS, Meyer RD, Armstrong D: *Pseudomonas aeruginosa* vaccine in cancer patients. Ann Intern Med 1973; 79:518-527

94. Alexander JW, Fisher MW: Immunological determinants of *Pseudomonas* infections of man accompanying severe burn injury. J Trauma 1970; 10:565-574

95. Polk HC, Borden S, Aldrete JA: Prevention of *Pseudomonas* respiratory infection in a surgical intensive care unit. Ann Surg 1973; 177:607-614

96. Pennington JE, Reynolds HY, Wood RE, et al: Use of a *Pseudomonas aeruginosa* vaccine in patients with acute leukemia and cystic fibrosis. Am J Med 1975; 58:629-636

97. Jones RL, Roe EA: Low mortality in burned patients in a *Pseudomonas* vaccine trial. Lancet 1978; 2:401-403

98. Jones RJ, Gupta JL, Roe EA: Controlled trials of a polyvalent *Pseudomonas* vaccine in burns. Lancet 1979; 2:977-982

99. Braude AI, Ziegler EJ, McCutchan JA, et al: Immunization against nosocomial infection. Am J Med 1981; 70:463-466

100. Ziegler EJ, McCutchan JA, Fierer J, et al: Treatment of gram-negative bacteremia and shock with human antiserum to a mutant *Escherichia coli*. N Engl J Med 1982; 307:1225-1230

ON RATIONING OF HEALTH CARE

AS RISING HEALTH EXPENDITURES in the United States constitute a growing proportion of the nation's economic output, driven by factors such as the development of improved medical technology and the aging of the population, public policymakers are reassessing the scope of government health care financing in light of competing public funding priorities. Actions already initiated to limit or reduce economic resources allocated to health care have given rise to the possibility that some form of explicit rationing of medical services may be forced upon society in the near future. Resource allocation decisions made by government and other third-party payors may cause drastic cost-cutting measures within the health care delivery system, which in turn may result in the rationing of services to patients as the availability of or access to those services is diminished.

Practicing physicians are faced with the dilemma of attempting to serve the societal goals of high quality medical care, equity of access to care and health care cost containment—goals that may in fact conflict with one another. Pressures exerted by hospitals, government and third-party payors threaten to cast physicians as agents of rationing in strategies intended only to curtail escalating health care costs.

Given the far-reaching ethical, political and social implications of policies concerning the rationing of scarce medical resources, decisions in this regard must be reached through a process involving full participation by all concerned sectors of society. Physicians, by virtue of their medical expertise and their central role in the health care delivery system, must play an important role in the development of such a broad-based consensus, but cannot be expected to assume total responsibility for the equitable disbursement of society's limited health resources. The medical profession does, however, have a clear responsibility in helping to obviate, to the greatest possible extent, the necessity of explicit rationing schemes. Efforts toward this end include the promotion of technology assessment to develop information on the benefits and costs of alternative treatments, the elimination of inappropriate or unnecessary treatments and procedures, better communication with patients regarding the relative benefits and costs of alternative interventions and utilization of the least expensive settings for the safe and efficient delivery of high quality medical care. Incorporation of greater emphasis on preventive medicine in clinical practice also must be encouraged as an appropriate cost-containment measure.

While the medical profession cannot abdicate its responsibility to society in addressing the need to control health care costs, the individual physician's primary and overriding responsibility is to his or her patients. In the care and treatment of patients, a physician must be guided by decisions based on the informed consent of patients to whatever therapies are clearly and proportionately beneficial to them. A physician has a duty to serve as an advocate of the patient's best interests and ought not become the sole responsible agent of institutional rationing schemes based on strictly fiscal considerations.

A policy statement from the Committee on Evolving Trends in Society Affecting Life, California Medical Association

Adopted by the CMA Council, August 23, 1985